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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (280 characters max)					
PEPTIDE DEFORMYLASE INHIBITORS					
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ENCLOSED APPLICATION PARTS (check all that apply)			
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<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT (\$)	\$160.00

Respectfully submitted,
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Date:

8/15/03

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37,444

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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20462

CUSTOMER NUMBER

PEPTIDE DEFORMYLASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to the use of novel antibacterial compounds, and
 5 pharmaceutical compositions containing these compounds as peptide deformylase inhibitors.

BACKGROUND OF THE INVENTION

Bacterial initiator methionyl tRNA is modified by methionyl tRNA formyltransferase
 (FMT) to produce formyl-methionyl tRNA. The formyl methionine (f-met) is then
 10 incorporated at the N-termini of newly synthesized polypeptides. Polypeptide deformylase
 (PDF or Def) then deformylates primary translation products to produce N-methionyl
 polypeptides. Most intracellular proteins are further processed by methionine amino peptidase
 (MAP) to yield the mature peptide and free methionine, which is recycled. PDF and MAP are
 both essential for bacterial growth, and PDF is required for MAP activity. This series of
 15 reactions is referred to as the methionine cycle (Figure 1).

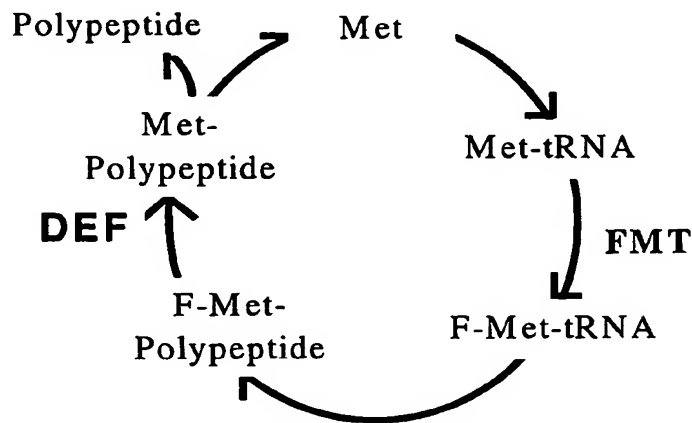


Figure 1. The methionine cycle.

20 To date, polypeptide deformylase homologous genes have been found in bacteria, in
 chloroplast-containing plants, in mice and in humans. The plant proteins are nuclear encoded

but appear to carry a chloroplast localisation signal. This is consistent with the observation that chloroplast RNA and protein synthesis processes are highly similar to those of eubacteria. While there is limited information on protein expression of mammalian PDF gene homologs (Bayer Aktiengesellschaft, Pat. WO2001/42431), no functional role for such proteins has been demonstrated to date (Meinzel, T., Parasitology Today 16(4), 165-168, 2000).

Polypeptide deformylase is found in all eubacteria for which high coverage genomic sequence information is available. Sequence diversity among PDF homologs is high, with as little as 20% identity between distantly related sequences. However, conservation around the active site is very high, with several completely conserved residues, including one cysteine and two histidines which are required to coordinate the active site metal (Meinzel, T. et al., J. Mol. Biol. 267, 749-761, 1997).

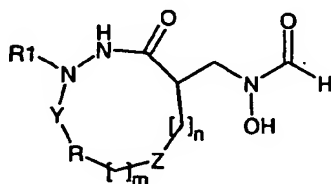
PDF is recognized to be an attractive antibacterial target, as this enzyme has been demonstrated to be essential for bacterial growth in vitro (Mazel, D. et al., EMBO J. 13 (4), 914-923, 1994), is not believed to be involved in eukaryotic protein synthesis (Rajagopalan et al., J. Am. Chem. Soc. 119, 12418-12419, 1997), and is universally conserved in prokaryotes (Kozak, M., Microbiol. Rev. 47, 1-45, 1983). Therefore PDF inhibitors can potentially serve as broad spectrum antibacterial agents.

SUMMARY OF THE INVENTION

The present invention involves novel antibacterial compounds represented by Formula (1) hereinbelow and their use as PDF inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect of the present invention, there is provided a compound of formula (1):



(1)

wherein:

Y represents $-\text{C}(\text{O})-$ or a covalent bond;

R represents a substituted arylene, a substituted heteroarylene or a covalent bond;

Z represents $-\text{CH}_2-$, $-\text{NR}_3-$, $-\text{O}-$, $-\text{C}(\text{O})\text{NR}_3-$, $-\text{NR}_3\text{C}(\text{O})-$ or $-\text{CH}=\text{CH}-$ when R is a

5 substituted arylene or a substituted heteroarylene, and represents $-\text{CH}_2-$ or $-\text{CH}=\text{CH}-$ when R is a covalent bond; R_3 is hydrogen, C_{1-3} substituted alkyl, and $(\text{CH}_2)_{0-2}-\text{C}_{3-6}$ substituted carbocycle;

R_1 is selected from the group consisting of:

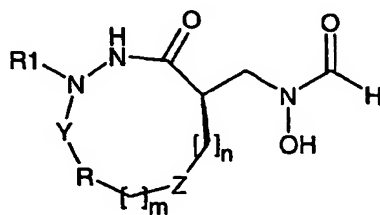
10 hydrogen, C_{1-3} substituted alkyl, C_{2-3} substituted alkenyl, C_{2-3} substituted alkynyl, and $(\text{CH}_2)_{0-2}-\text{C}_{3-6}$ substituted carbocycle;

m is equal to 0 when $\text{Z} = -\text{NR}_3-$ or $-\text{CH}_2-$; or m is equal to 0 or 1 when $\text{Z} = -\text{O}-$, $-\text{C}(\text{O})\text{NR}_3-$ or $-\text{NR}_3\text{C}(\text{O})-$; or m is an integer between 0 and 6 when $\text{Z} = -\text{CH}=\text{CH}-$;

15 n is an integer equal to or greater than 2, appropriately chosen so that the number of atoms in the macrocyclic ring ranges from 13 to 16;

or a salt, solvate, or physiologically functional derivative thereof.

In this invention the most preferred R_1 group is hydrogen. In this invention the most preferred absolute configuration of compounds of the formula (1) is indicated below:



20

As used herein, the term “alkyl” refers to a straight or branched chain saturated hydrocarbon radical. Examples of “alkyl” as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like.

25

As used herein, the term “substituted alkyl” refers to a straight or branched chain saturated hydrocarbon radical, optionally substituted with substituents selected from the group that includes C_{1-3} alkyl (optionally substituted by one to three fluorines), C_{2-3} alkenyl, C_{2-3}

alkynyl, C₁₋₂ alkoxy (optionally substituted by one to three fluorines), sulfanyl, sulfinyl, sulfonyl, oxo, hydroxy, mercapto, amino, guanidino, carboxy, aminocarbonyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, aminosulfonyl, sulfonylamino, carboxyamido, ureido, nitro, cyano and halogen, multiple degrees of substitution being allowed.

5 As used herein, the term "alkenyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl and propenyl.

As used herein, the term "substituted alkenyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond, optionally substituted
10 with substituents selected from the group which includes C₁₋₃ alkyl (optionally substituted by one to three F), amino, aryl, cyano and halogen, multiple degrees of substitution being allowed.

As used herein, the term "alkynyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond. Examples of "alkynyl" as used herein
15 include, but are not limited to, acetylenyl and 1-propynyl.

As used herein, the term "substituted alkynyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond, optionally substituted with substituents selected from the group which includes C₁₋₃ alkyl (optionally substituted by one to three F), amino, aryl and halogen, multiple degrees of substitution being allowed.

20 As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I), and "halo" refers to the halogen radicals fluoro, chloro, bromo and iodo.

As used herein, the term "carbocycle" refers to a non-aromatic cyclic hydrocarbon radical having from three to seven carbon atoms. For carbocycles with five- to seven-membered rings, a ring double bond is allowed. Exemplary "carbocycle" groups include, but
25 are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, and cycloheptyl.

As used herein, the term "substituted carbocycle" refers to a non-aromatic cyclic hydrocarbon radical having from three to seven carbon atoms, and which is optionally substituted with substituents selected from the group which includes C₁₋₃ alkyl (optionally substituted by one to three F), C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₂ alkoxy (optionally substituted
30 by one to three F), sulfanyl, sulfinyl, sulfonyl, oxo, hydroxy, mercapto, amino, guanidino,

carboxy, aminocarbonyl, aryl, aryloxy, heteroaryl, heterocyclic, aminosulfonyl, sulfonylamino, carboxyamide, nitro, ureido, cyano and halogen, multiple degrees of substitution being allowed. For carbocycles with five- to seven-membered rings, a ring double bond is allowed.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted benzene ring fused to one or more optionally substituted benzene rings to form a ring system. Exemplary optional substituents include C₁₋₃ substituted alkyl, C₂₋₃ substituted alkenyl, C₂₋₃ substituted alkynyl, heteroaryl, heterocyclic, aryl, C₁₋₃ alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxyamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen, or ureido, multiple degrees of substitution being allowed. Such a ring or ring system may be optionally fused to one or more optionally substituted aryl rings (including benzene rings), carbocycle rings or heterocyclic rings. Examples of "aryl" groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, biphenyl, or indanyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" refers to an optionally substituted benzene ring diradical or to an optionally substituted benzene ring fused to one or more optionally substituted benzene rings to form a ring system diradical. Exemplary optional substituents include C₁₋₃ substituted alkyl, C₂₋₃ substituted alkenyl, C₂₋₃ substituted alkynyl, heteroaryl, heterocyclic, aryl, C₁₋₃ alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxyamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen, or ureido, multiple degrees of substitution being allowed. Such a ring or ring system may be optionally fused to one or more optionally substituted aryl rings (including benzene rings), carbocycle rings or heterocyclic rings. Examples of "arylene" groups include, but are not limited to, phenylene, naphthylene, tetrahydronaphthylene, biphenylene or indanylene, as well as substituted derivatives thereof.

As used herein, the term "heteroarylene" refers to an optionally substituted monocyclic five to six membered aromatic ring diradical containing one or more heteroatoms selected from S, SO, SO₂, O, N, or N-oxide, or to an optionally substituted polycyclic aromatic diradical consisting of an aromatic ring fused to one or more optionally substituted rings, such

as heteroaryl rings, aryl rings, heterocyclic rings, or carbocycle rings (e.g., a bicyclic or tricyclic ring system). Examples of optional substituents are selected from the group which includes C₁₋₃ substituted alkyl, C₂₋₃ substituted alkenyl, C₂₋₃ substituted alkynyl, heteroaryl, heterocyclic, aryl, C₁₋₃ alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen or ureido, multiple degrees of substitution being allowed. Examples of "heteroarylene" groups used herein include, but are not limited to, pyrimidin-2,6-ylene, pyrimidin-2,4-ylene, pyrimidin-4,6-ylene and 1,3,5-triazin-2,4-ylene, and substituted versions thereof.

As used herein, the term "heteroaryl" refers to an optionally substituted monocyclic five to six membered aromatic ring containing one or more heteroatoms selected from S, SO, SO₂, O, N, or N-oxide, or to such an aromatic ring fused to one or more optionally substituted rings, such as heteroaryl rings, aryl rings, heterocyclic rings, or carbocycle rings (e.g., a bicyclic or tricyclic ring system). Examples of optional substituents are selected from the group which includes C₁₋₃ substituted alkyl, C₂₋₃ substituted alkenyl, C₂₋₃ substituted alkynyl, heteroaryl, heterocyclic, aryl, C₁₋₃ alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen or ureido, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include, but are not limited to, benzoimidazolyl, benzothiazolyl, benzoisothiazolyl, benzothiophenyl, benzopyrazinyl, benzotriazolyl, benzotriazinyl, benzo[1,4]dioxanyl, benzofuranyl, 9*H*-*a*-carbolinyl, cinnolinyl, 2,3-dihydro-[1,4]dioxino[2,3-*b*]-pyridinyl, furanyl, furo[2,3-*b*]pyridinyl, imidazolyl, imidazolidinyl, imidazopyridinyl, isoxazolyl, isothiazolyl, isoquinolinyl, indolyl, indazolyl, indolizinyl, naphthyridinyl, oxazolyl, oxothiadiazolyl, oxadiazolyl, phthalazinyl, pyrrolyl, purinyl, pteridinyl, phenazinyl, pyrazolyl, pyridyl, pyrazolopyrimidinyl, pyrazolopyridinyl, pyrrolizinyl, pyridazyl, pyrazinyl, pyrimidyl, 4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2-*i*]-quinolin-4-yl, quinoxalinyl, quinazolinyl, quinolinyl, quinolizinyl, thiophenyl, triazolyl, triazinyl, tetrazolopyrimidinyl, triazolopyrimidinyl, tetrazolyl, thiazolyl, thiazolidinyl, and substituted versions thereof.

As used herein, the term "heterocyclic" refers to a three to seven-membered ring containing one or more heteroatoms selected from S, SO, SO₂, O, N, or N-oxide, optionally substituted with substituents selected from the group which includes C₁₋₃ substituted alkyl, C₂₋₃ substituted alkenyl, C₂₋₃ substituted alkynyl, heteroaryl, heterocyclic, aryl, C₁₋₃ alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxyamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen, or ureido, multiple degrees of substitution being allowed. Such a ring can be saturated or have one or more degrees of unsaturation. Such a ring may be optionally fused to one or more other optionally substituted "heterocyclic" ring(s), aryl ring(s), heteroaryl ring(s), or carbocycle ring(s). Examples of "heterocyclic" moieties include, but are not limited to, 1,4-dioxanyl, 1,3-dioxanyl, pyrrolidinyl, pyrrolidin-2-onyl, piperidinyl, imidazolidine-2,4-dione piperidinyl, piperazinyl, piperazine-2,5-dionyl, morpholinyl, dihydropyranyl, dihydrocinnolyl, 2,3-dihydrobenzo[1,4]dioxinyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, tetrahydropyranyl, 2,3-dihydrofuranlyl, 2,3-dihydrobenzofuranlyl, dihydroisoxazolyl, tetrahydrobenzodiazepinyl, tetrahydroquinolinyl, tetrahydrofuranlyl, tetrahydronaphthyridinyl, tetrahydropurinyl, tetrahydrothiopyranyl, tetrahydrothiophenyl, dihydroquinoxalinyl, tetrahydroquinoxalinyl, tetrahydropyridinyl, tetrahydrocarbolinyl, 4H-benzo[1,3]-dioxinyl, benzo[1,3]dioxonyl, 2,2-difluorobenzo-[1,3]-dioxonyl, 2,3-dihydro-phthalazine-1,4-dionyl, isoindole-1,3-dionyl, and the like.

As used herein, the term "alkoxy" refers to the group -OR_a, where R_a is alkyl as defined above. Exemplary alkoxy groups useful in the present invention include, but are not limited to, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy.

As used herein the term "aralkoxy" refers to the group -OR_aR_b, where R_a is alkyl and R_b is aryl as defined above.

As used herein the term "aryloxy" refers to the group -OR_a, where R_a is aryl as defined above.

As used herein, the term "mercapto" refers to the group -SH.

As used herein, the term "sulfanyl" refers to the group -SR_a, where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term “sulfinyl” refers to the group $-S(O)R_a$, where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term “sulfonyl” refers to the group $-S(O)_2R_a$, where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

5 As used herein, the term “oxo” refers to the group $=O$.

As used herein, the term “hydroxy” refers to the group $-OH$.

As used herein, the term “amino” refers to the group $-NH_2$. The amino group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

10 As used herein, the term “cyano” refers to the group $-CN$.

As used herein, the term “aminosulfonyl” refers to the group $-S(O)_2NH_2$. The aminosulfonyl group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

15 As used herein, the term “sulfonylamino” refers to the group $-NHS(O)_2R_a$ where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term “carboxyamido” refers to the group $-NHC(O)R_a$ where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

20 As used herein, the term “carboxy” refers to the group $-C(O)OH$. The carboxy group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term “aminocarbonyl” refers to the group $-C(O)NH_2$. The aminocarbonyl group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

25 As used herein, the term “ureido” refers to the group $-NHC(O)NHR_a$ wherein R_a is hydrogen, alkyl, carbocycle or aryl as defined above.

As used herein, the term “guanidino” refers to the group $-NHC(=NH)NH_2$.

As used herein, the term “acyl” refers to the group $-C(O)R_a$, where R_a is alkyl, carbocycle, or heterocyclic as defined herein.

30 As used herein, the term “aroyl” refers to the group $-C(O)R_a$, where R_a is aryl as defined herein.

As used herein, the term "heteroaroyl" refers to the group $-C(O)R_a$, where R_a is heteroaryl as defined herein.

As used herein, the term "acyloxy" refers to the group $-OC(O)R_a$, where R_a is alkyl, carbocycle, or heterocyclic as defined herein.

5 As used herein, the term "aroyloxy" refers to the group $-OC(O)R_a$, where R_a is aryl as defined herein.

As used herein, the term "heteroaroyloxy" refers to the group $-OC(O)R_a$, where R_a is heteroaryl as defined herein.

Also included in the present invention are pharmaceutically acceptable salts and
10 complexes, such as the hydrochloride, hydrobromide and trifluoroacetate salts and the sodium, potassium and magnesium salts. The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

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Preferred compounds useful in the present invention are selected from the group consisting of:

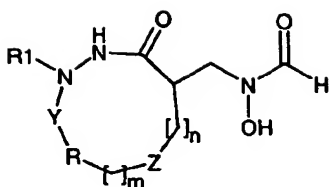
- N-{[(5R)-16-(Dimethylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-
1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide;
- 20 N-{[(5R)-16-(4-Morpholinyl)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-
1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide;
- N-{[(5R)-16-(Cyclopropylamino)-4-oxo-2,3,15,17,18-
pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl)methyl]-N-
hydroxyformamide;
- 25 N-{[(5R)-16-(4-Morpholinyl)-4-oxo-2,3,17,18-tetraazabicyclo[12.3.1]octadeca-
1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide;
- N-{[(5R)-16-Methyl-4-oxo-2,3,17,18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-
trien-5-yl)methyl]-N-hydroxyformamide;
- 30 N-{[(5R)-4-Oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-
yl)methyl]-N-hydroxyformamide;

N-{[(5R)-15-Methyl-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide;
 N-{[(5R)-15-(4-Morpholinyl)-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide;
 5 N-{[(5R)-15-(2-Furanyl)-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide;
 N-{[(5R)-15-(4-Morpholinyl)-4-oxo-2,3,14,16,17-pentaazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide;
 10 N-{[(5R)-15-(Dimethylamino)-4-oxo-2,3,14,16,17-pentaazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide;
 N-{[(5R)-4-Oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl}-N-hydroxyformamide;
 N-{[(5R)-14-Methyl-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl}-N-hydroxyformamide;
 15 N-{[(5R)-14-(Dimethylamino)-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl}-N-hydroxyformamide;
 N-{[(5R)-14-(4-Morpholinyl)-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl}-N-hydroxyformamide; and
 N-{[(4R)-3,15-Dioxo-1,2-diazacyclopentadecan-4-yl)methyl}-N-hydroxyformamide.

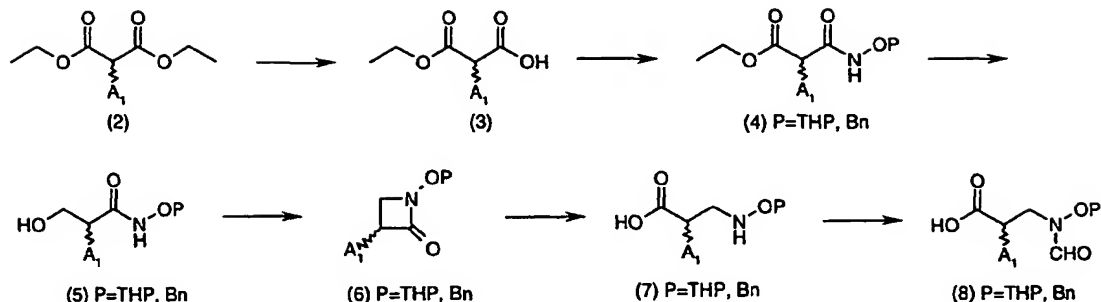
GENERAL SYNTHETIC SEQUENCE

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes, which are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

The present invention provides compounds of Formula (1) that can be prepared from the common racemic intermediate (8), or common chiral intermediates (17) and (25). Substituents A1 and A2 both contain a mono-, di- or trisubstituted olefin moiety. The olefins in A1 and A2 are appropriately chosen so that an intramolecular ring-closing metathesis (RCM) reaction combines A1 and A2, forming a macrocyclic structure.



(1)



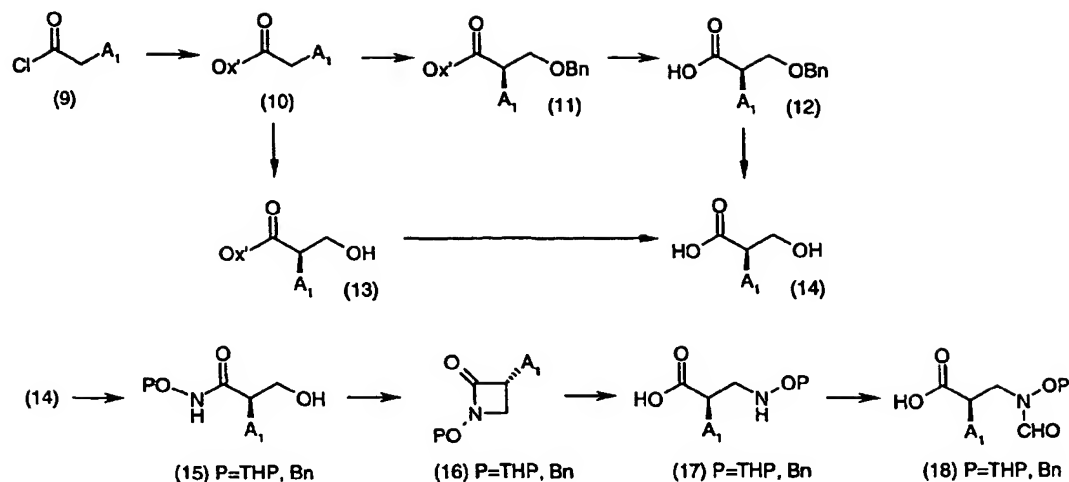
5 Scheme 1

As shown in Scheme 1, intermediate (8) can be prepared by reacting the mono-substituted dialkyl malonate (2) with a base, such as potassium hydroxide, in an appropriate solvent, such as ethanol/water, to afford the mono-acid (3). Coupling of (3) with O-benzylhydroxylamine or O-(tetrahydro-2H-pyran-2-yl)hydroxylamine in the presence of a coupling reagent, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), and a base, such as 4-dimethylaminopyridine (DMAP), in an appropriate solvent, such as dichloromethane, gives the amide (4), where P is benzyl or tetrahydro-2H-pyran-2-yl. Reduction of the ester functionality of compound (4) with a reducing agent, such as lithium borohydride, in an appropriate solvent, such as tetrahydrofuran, at room temperature provides the alcohol (5). Treatment of the alcohol (5) under Mitsunobu conditions affords the lactam (6). The same transformation may be achieved by treating (5) with triphenylphosphine, carbon tetrachloride and a base, such as triethylamine, to obtain (6). Hydrolysis of the lactam (6) using, for example, lithium hydroxide in an appropriate solvent mixture, such as THF-H₂O-MeOH, gives acid (7). Formylation of the amine group of (7) is achieved using formic acid and acetic anhydride in a solvent, such as dichloromethane, to provide the formylated compound (8).

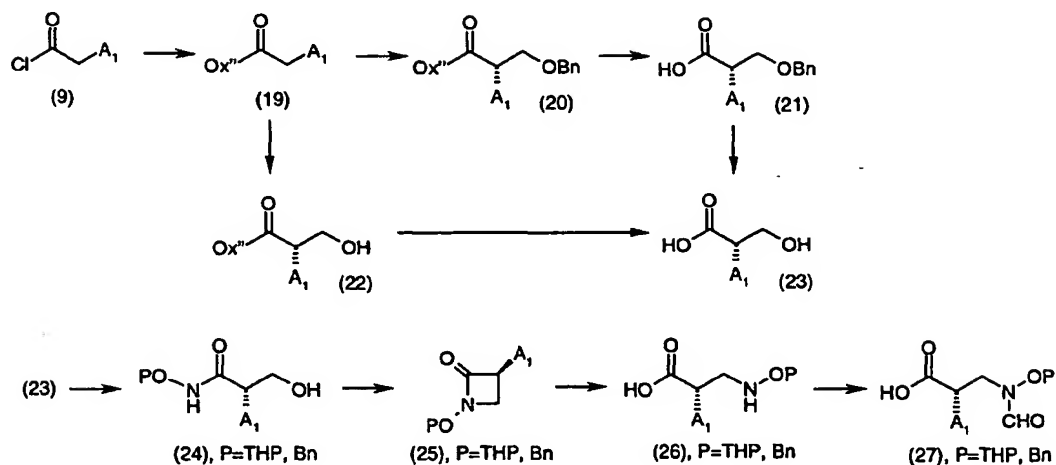
Any racemates can be resolved at the level of any intermediate during the synthesis or at the level of the final product using, for example, a chiral chromatography method, to provide compound (8) in each of two enantiomeric forms.

Alternatively, an enantiomer of intermediate (8), such as (18) in Scheme 2 or (27) in Scheme 3, can be prepared by reacting an appropriate acid chloride (9) with a chiral agent, such as Evans' chiral oxazolidinone, in the presence of a base, such as n-butyl lithium, to afford the chiral intermediate (10) in Scheme 2 or (19) in Scheme 3. Treatment of the compound (10) or (19) with a base, such as diisopropylethylamine, in the presence of a chelating agent, such as titanium tetrachloride, in a solvent, such as tetrahydrofuran, followed by addition of an electrophile, such as benzoxymethylchloride, provides either of two chiral compounds (11) or (20), depending on the selection of chiral auxiliary. Conversion of compound (11) or (20) to the corresponding hydroxyacid (14) or (23) can be achieved by a sequence comprising oxidative cleavage of the chiral oxazolidinone, using, for example H_2O_2 and lithium hydroxide, to the respective intermediates (12) or (21), followed by hydrogenolysis, to afford intermediates (13) or (21), respectively. Compounds (10) or (19) can also be converted to intermediates (14) or (23), respectively, in a two-step procedure. For this transformation, (10) or (19) can be treated with a base, such as diisopropylethylamine, in the presence of a chelating agent, such as titanium tetrachloride, in a solvent, such as tetrahydrofuran, followed by addition of trioxane or any other formaldehyde equivalent to provide compounds (13) or (22), which are then submitted to oxidative cleavage of the chiral oxazolidinone, using, for example H_2O_2 and lithium hydroxide, to the respective acids (14) or (23), respectively.

Coupling of the acid (14) or (23) with benzoxyamine or O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine in the presence of coupling agents, such as EDCI-DMAP, yields the amides (15) or (24), respectively. These can be cyclized to the azetidin-2-ones (16) or (25) using Mitsunobu conditions or a combination of triphenylphosphine-carbon tetrachloride-triethylamine. Hydrolysis of the azetidin-2-one (16) or (25), using for example lithium hydroxide, in an appropriate solvent, gives the corresponding acid (17) or (26), respectively. Conversion of compound (17) or (26) to the carboxylic acid (18) or (27) can be achieved using an appropriate formylating agent, such as formic acid/acetic anhydride or methyl formate, in neat reagents or in an appropriate solvent, such as dichloromethane.

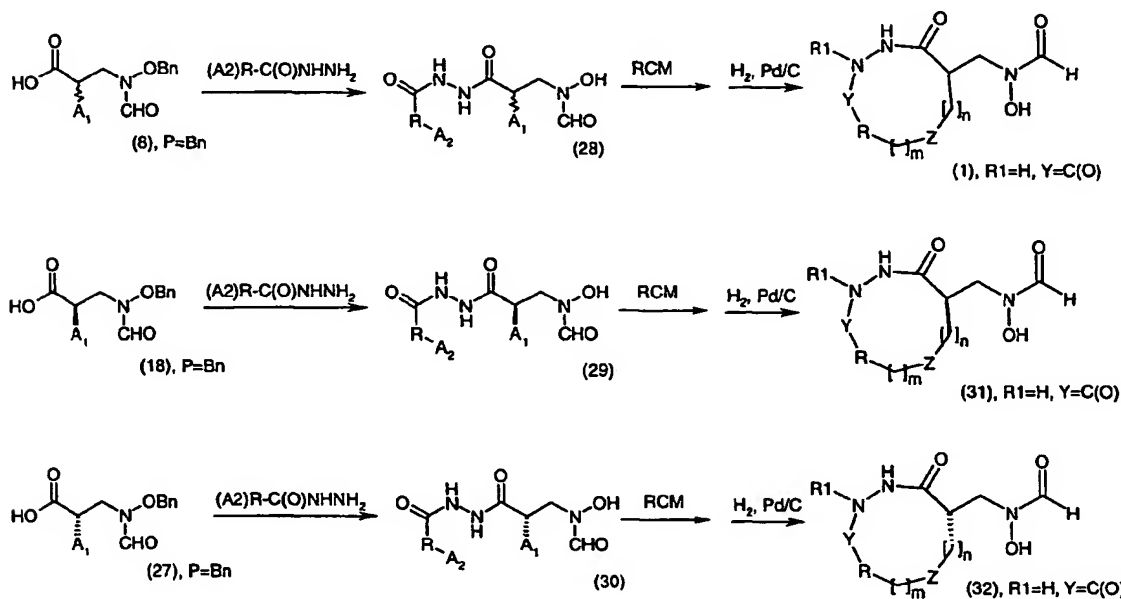
**Scheme 2**

5

**Scheme 3**

As shown in Scheme 4, compound (8) can be coupled to (A2)R-C(O)NHNH₂, using conditions such as DMAP-EDCI or EDCI-HOAt-NMM for example, to generate (28). Treatment of (28) with an RCM catalyst, such as one of Grubbs's ruthenium catalysts (tricyclohexylphosphine)-[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene]-[benzylidene]-ruthenium(IV) dichloride or bis(tricyclohexylphosphine)-[benzylidene]-ruthenium(IV) dichloride, in a solvent such as methylene chloride, followed by hydrogenation,

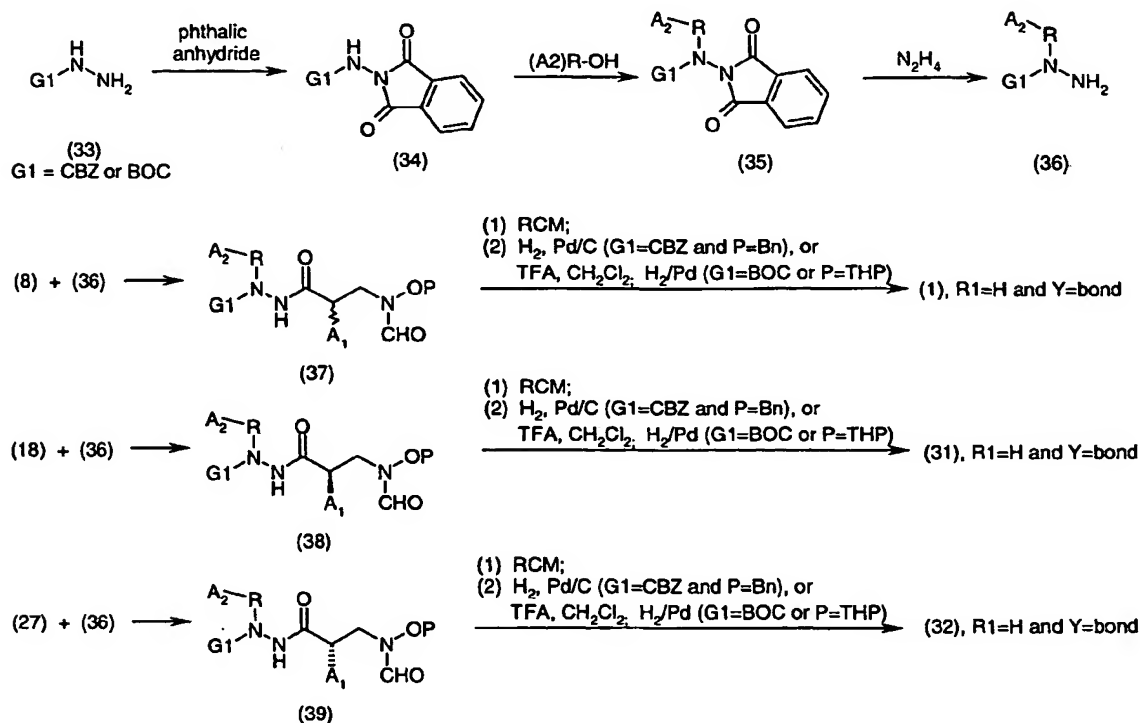
affords (1) where R1 is H and Y is C(O). Similarly, compounds (18) and (27) can be submitted to the same procedure to afford, respectively, (31) where R1 is H and Y is -C(O)-, and (32) where R1 is H and Y is -C(O)-.



Scheme 4

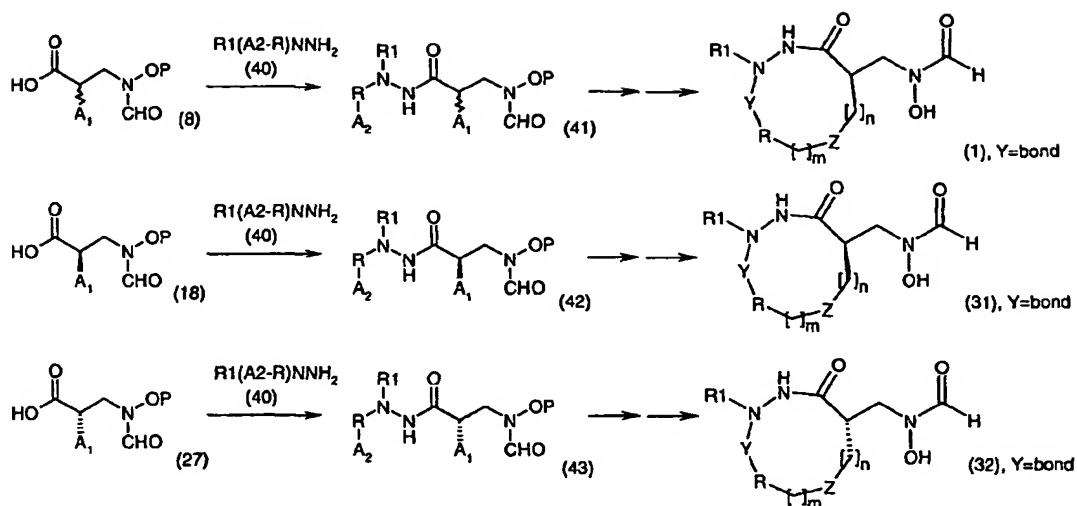
Alternatively, as shown in Scheme 5, the monoprotected hydrazine G1NHNH₂ (33), where G1 is benzoxycarbonyl or tert-butoxycarbonyl, can be reacted with phthalic anhydride to yield intermediate (34). (34) can be coupled to the alcohol (A2)R-OH under Mitsunobu conditions to yield (35), which upon hydrazinolysis originates hydrazine (36). Coupling of (36) to acid (8) using conditions such as DMAP/EDCI or EDCI/HOAt/NMM affords (37). (37) can be submitted to RCM (using, for example, one of Grubbs's ruthenium catalysts (tricyclohexylphosphine)-[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene]-[benzylidene]-ruthenium(IV) dichloride or bis(tricyclohexylphosphine)-[benzylidene]-ruthenium(IV) dichloride, in a solvent such as methylene chloride) to afford the corresponding cyclized product. When G1 is benzoxycarbonyl and P is benzyl, hydrogenation affords the desired product (1) where R1 is H and Y is a covalent bond. When G1 is tert-butoxycarbonyl or P is O-(tetrahydro-2H-pyran-2-yl), a combination of hydrogenation and acidic treatment affords the desired product (1) where R1 is H and Y is a covalent bond. Similarly, compounds

(18) and (27) can be submitted to the same procedure to afford, respectively, (31) where R1 is H and Y is a covalent bond, or (32) where R1 is H and Y is a covalent bond.



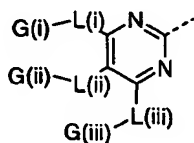
5 Scheme 5

As shown in Scheme 6, coupling of the acid (8) with the hydrazine R1(A₂-R)NNH₂ (40), using conditions such as DMAP-EDCI or EDCI-HOAt-NMM, provides the hydrazide (41). RCM (using, for example, one of Grubbs's ruthenium catalysts (tricyclohexylphosphine)-[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene]-[benzylidene]-ruthenium(IV) dichloride or bis(tricyclohexylphosphine)-[benzylidene]-ruthenium(IV) dichloride, in a solvent such as methylene chloride), followed by hydrogenation (using a catalyst, such as 10% Pd/C, in an appropriate solvent, such as ethanol) and acidic deprotection (only necessary if P is THP; 80% acetic acid-water at room temperature or 40 °C, for example) gives the desired compound (1). Similarly, coupling of the chiral acid (18) or (27) with the hydrazine (40) provides the corresponding hydrazide (42) or (43). RCM followed by hydrogenation and acidic treatment (if P is THP) gives the final desired compound (31) or (32).

**Scheme 6**

5 Hydrazines of general structure $R1(A2-R)NNH_2$ (40) may be purchased from available commercial sources or prepared according to literature methods by those skilled in the art. The following examples of specific structures of hydrazine (40) and the synthetic methods used to generate them are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

10 Hydrazines (40) where R1 is alkyl or hydrogen, and (A2)R has the general structure (44) may be prepared from appropriate precursors shown in Scheme 7, 8 and 9.



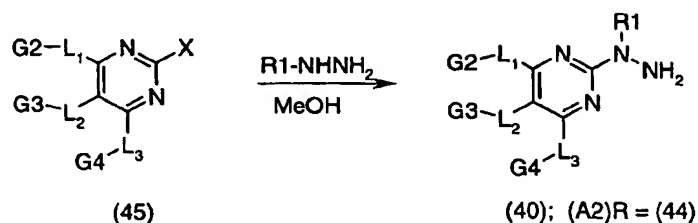
(44)

15

As shown in Scheme 7, hydrazine (40) where (A2)R is (44) can be prepared from precursor (45) by treatment with an appropriate hydrazine, such as hydrazine monohydrate, in an appropriate solvent, such as methanol. Alternatively, as shown in Scheme 8, hydrazine (40) where (A2)R is (44) can be prepared from precursor (46) by oxidation to the sulfone via treatment with an appropriate oxidant such as meta-chloroperoxybenzoic acid (m-CPBA) in an

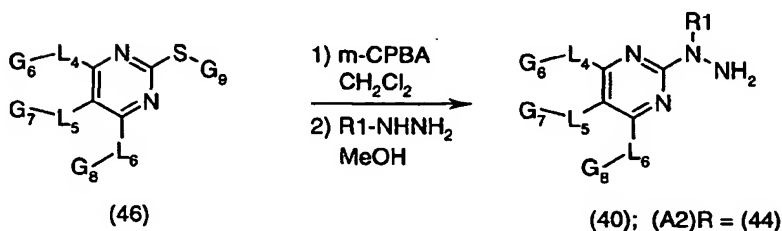
20

appropriate solvent such as methylene chloride. Further treatment with an appropriate hydrazine, such as hydrazine monohydrate, in an appropriate solvent, such as methanol, then provides the desired product (40) where (A2)R is (44). Alternatively, as shown in Scheme 9, hydrazine (40) where (A2)R is (44) can be prepared from (47) via treatment with sodium nitrate in an appropriate solvent such as aqueous sulfuric acid to give (48). Compound (48) is then treated with an appropriate halogenating reagent such as phosphorus oxychloride at reflux followed by treatment with an appropriate hydrazine, such as hydrazine monohydrate, in an appropriate solvent, such as methanol, to provide intermediate (40) where (A2)R is (44). Compounds (45), (46), (47) and (48) are available from commercial sources, or can be prepared via literature methods by those skilled in the art (Pyrimidines. Brown, D.J. In "The Chemistry of Heterocyclic Compounds" vol. 52, Taylor, E.C., ed.; Wiley: New York, 1994).



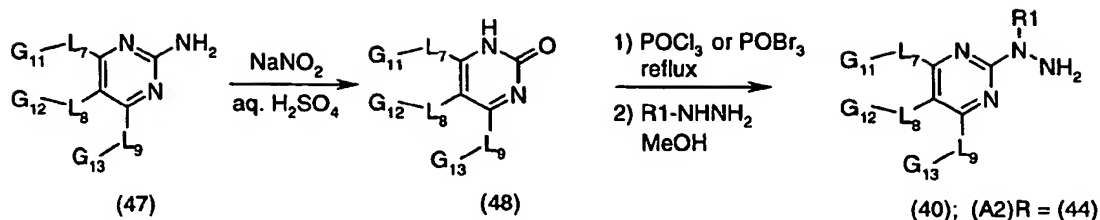
X = halogen; L1, L2, L3 = bond, N-G5, O;
G2, G3, G4, G5 = H, Alkyl, Alkenyl, Acyl, Heterocyclic, Aryl, Heteroaryl;
either G2 or G4 displays a double bond suitable for participation in RCM.

Scheme 7



L4, L5, L6 = bond, N-G10, O;
G6, G7, G8, G10 = H, Alkyl, Alkenyl, Acyl, Heterocyclic, Aryl, Heteroaryl; G9 = Alkyl, Aryl;
either G6 or G8 displays a double bond suitable for participation in RCM.

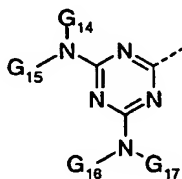
Scheme 8



L7, L8, L9 = bond, O;
 G11, G12, G13 = H, Alkyl, Alkenyl, Acyl, Heterocyclic, Aryl, Heteroaryl;
 either G11 or G13 displays a double bond suitable for participation in RCM.

Scheme 9

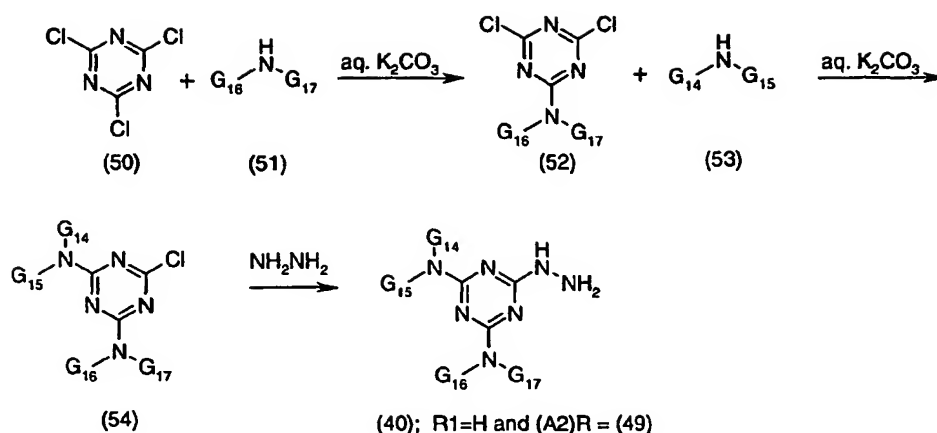
Hydrazines (40) where R1 is hydrogen and (A2)R has the general structure (49) may be prepared following procedures outlined in Scheme 10.



G14, G15, G16, G17 = H, alkyl, alkenyl, aryl, heteroaryl, heterocyclic;

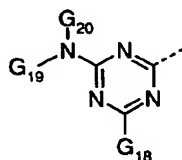
either G16 or G17 displays a double bond suitable for participation in RCM.

As shown in Scheme 10, cyanuric chloride (50) may be treated with one equivalent of amine (51) under mild conditions, such as 0 °C in acetone in the presence of aqueous potassium carbonate, to afford (52). Treatment of (52) with amine (53) under conditions such as 25 °C in acetone in the presence of potassium carbonate yields (54). Displacement of the remaining chloride in (54) with hydrazine affords (40) where R1 is H and (A2)R is (49).



Scheme 10

Hydrazines (40) where R1 is hydrogen and (A2)R has the general structure (55) may be prepared following procedures outlined in Scheme 11 (Menicagli, R. et al., Tetrahedron 56, 9705-9711, 2000).

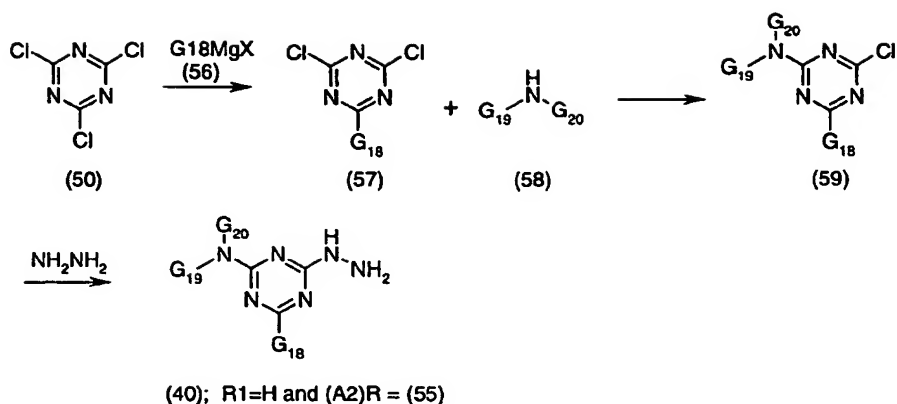


(55)

G19, G20 = H, alkyl, alkenyl, aryl, heteroaryl, heterocyclic;

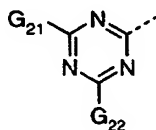
G18 = alkenyl, containing a double bond suitable for participation in RCM.

As shown in Scheme 11, cyanuric chloride (50) may be reacted with the Grignard compound (56) to form (57), which upon treatment with amine (58) affords monochloride (59). Hydrazinolysis of (59) yields (40) where R1 is H and (A2)R is (55).



Scheme 11

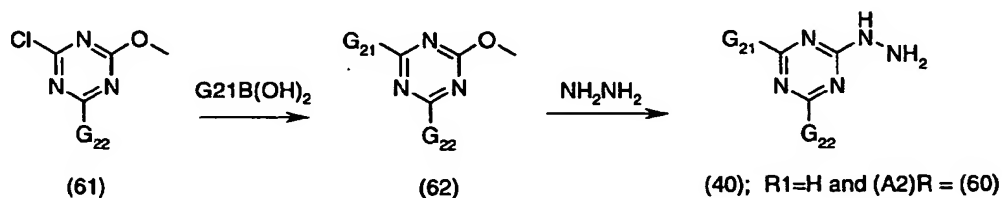
Hydrazines (40) where R1 is hydrogen and (A2)R has the general structure (60) may be prepared following procedures outlined in Scheme 12 (Kobe, J. et al., Monatsh. Chem. 101, 724-735, 1970; Janietz, D. and Bauer, M., Synthesis 33-34, 1993).



(60)

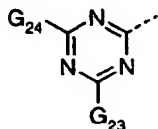
- 10 G21 = aryl, heteroaryl; G22 = alkenyl, aryl, heteroaryl, heterocyclic;
G22 displays a double bond suitable for participation in RCM.

As shown in Scheme 12, compound (61) may be coupled to boronic acid G21B(OH)₂ or equivalent under Suzuki coupling protocols to afford (62), which upon hydrazinolysis yields (40) where R1 is H and (A2)R is (60).



Scheme 12

Hydrazines (40) where R1 is hydrogen and (A2)R has the general structure (63) may be prepared following procedures outlined in Scheme 13.

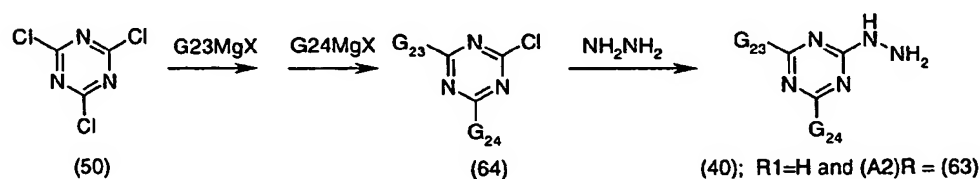


5 (63)

G23, G24 = alkyl, alkenyl, heterocyclic;

either G23 or G24 contains a double bond suitable for participation in RCM.

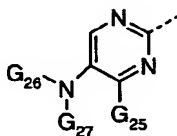
As shown in Scheme 13, sequential reaction of cyanuric chloride (50) with Grignard
10 compounds G23MgX and G24MgX in a solvent such as benzene affords monochloride (64),
which can be treated with hydrazide to afford (40) where R1=H and (A2)R=(63).



Scheme 13

15

Hydrazines (40) where R1 is hydrogen and (A2)R has the general structure (65) may be prepared following procedures outlined in Scheme 14.



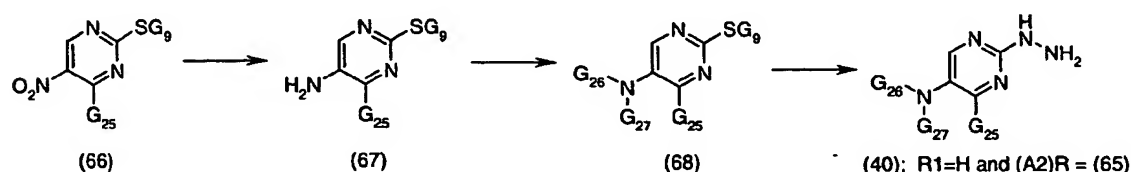
20 (65)

G26 = alkyl, aryl, heteroaryl, heterocyclic;

G27 = hydrogen, alkyl, aryl, heteroaryl, heterocyclic;

G25 = alkenyl, containing a double bond suitable for participation in RCM.

As shown in Scheme 14, (66) can be reduced to (67) using reducing conditions such as iron and acetic acid. Sequential treatment of (67) with alkylating agents G26X and G27X (where X is halide or trifluoromethylsulfonate) affords (68). Alternatively, treatment of (67) with one equivalent of G26X affords (68) where G27 is H. Oxidation of (68) to the corresponding sulfoxide or sulfone using as oxidant such as meta-chloro perbenzoic acid, and subsequent treatment with hydrazine affords (40) where R1 is H and (A2)R is (65).



Scheme 14

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hz (Hertz);

T_R (retention time);

MeOH (methanol);

EtOH (ethanol);

TFA (trifluoroacetic acid);

DMSO (dimethylsulfoxide);

DCM (dichloromethane);

CDI (1,1-carbonyldiimidazole);

TLC (thin layer chromatography);

RP (reverse phase);

i-PrOH (isopropanol);

TEA (triethylamine);

THF (tetrahydrofuran);

AcOEt or EtOAc (ethyl acetate);

DMF (*N,N*-dimethylformamide);

HOAc (acetic acid);

HOSu (*N*-hydroxysuccinimide); Ac (acetyl);
 HOBT (1-hydroxybenzotriazole); BOC (*tert*-butoxycarbonyl);
 mCPBA (meta-chloroperbenzoic acid); FMOC (9-fluorenylmethoxycarbonyl);
 DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl);
 5 NMM (N-methyl morpholine); HOAt (1-hydroxy-7-azabenzotriazole);
 DMAP (4-dimethylaminopyridine); Bn (benzyl);
 TBAF (tetra-*n*-butylammonium fluoride); THP (tetrahydro-2H-pyran-2-yl)
 HPLC (high pressure liquid chromatography);
 BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
 10 EDCI (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride);
 HBTU (O-Benzotriazole-1-yl-N,N,N',N'- tetramethyluronium hexafluorophosphate).

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees
 15 Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are highest available purity unless otherwise indicated.

¹H NMR (hereinafter also "NMR") spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, a Bruker AVANCE-400, a General Electric QE-300 or a Bruker AM 400 spectrometer. Chemical shifts are expressed in parts
 20 per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

Mass spectra were run on an open access LC-MS system using electrospray ionization. LC conditions: 4.5% to 90% CH₃CN (0.02% TFA) in 3.2 min with a 0.4 min hold
 25 and 1.4 min re-equilibration; detection by MS, UV at 214 nm, and a light scattering detector (ELS). Column: 1 X 40 mm Aquasil (C18).

For preparative (prep) hplc; ca 50 mg of the final products were injected in 500 uL of DMSO onto a 50 X 20 mm I. D. YMC CombiPrep ODS-A column at 20 mL/min with a 10 min gradient from 10% CH₃CN (0.1% TFA) to 90% CH₃CN (0.1% TFA) in H₂O (0.1% TFA)
 30 and a 2 min hold. Flash chromatography was run over Merck Silica gel 60 (230 - 400 mesh).

Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution.

5 The following synthetic schemes are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

The compounds disclosed in Examples 2 to 16 were prepared following the general procedures described in Example 1.

10

Intermediate 1

(4S)-3-(7-Octenoyl)-4-benzyl-1,3-oxazolidin-2-one.

To a solution of (S)-(-)-4-benzyl-2-oxazolidinone (12.4 g, 69.79 mmol) in THF (200 mL) at -78 °C was added dropwise n-BuLi (30.7 mL, 2.5M solution in hexane, 76.77 mmol). After
15 stirring for 30 min at the same temperature, the reaction mixture was then treated with 7-octenoyl chloride (11.21 g, 69.79 mmol). The reaction mixture was stirred and allowed to warm to 10 °C over 5 h, and then quenched with saturated aqueous NH₄Cl solution (200 mL). The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine, and dried over MgSO₄. Removal of the solvent under reduced pressure
20 yielded the title compound. MH⁺ 302.

Intermediate 2

(4S)-3-[(2R)-2-Hydroxymethyl-7-octenoyl]-4-benzyl-1,3-oxazolidin-2-one.

To a solution of (4S)-3-(7-octenoyl)-4-benzyl-1,3-oxazolidin-2-one (2.24 g, 7.59 mmol) and
25 titanium (IV) chloride (1M in dichloromethane, 8.0 mL, 7.97 mmol) in dichloromethane (35 mL) at 0 °C was added dropwise diisopropylethylamine (1.5 mL, 8.35 mmol). After stirring at 0 °C for 1 hour, the resulting titanium enolate was then reacted with a solution of trioxane (0.82 g, 9.11 mmol) in dichloromethane (7 mL), followed by the addition of a solution of titanium (IV) chloride (1M in dichloromethane, 8.0 mL, 7.97 mmol). The reaction mixture
30 was then stirred at 0 °C for 4 h. The reaction mixture was then quenched with saturated ammonium chloride (50 mL). The aqueous layer was extracted with dichloromethane (100 mL).

x 2). The organic extracts were washed with brine, and dried over MgSO_4 , filtered and concentrated in vacuo to yield the title compound. MH^+ 332.

Intermediate 3

5 (2R)-2-(Hydroxymethyl)-7-octenoic acid.

A 0.05 M solution of (4S)-3-[(2R)-2-(hydroxymethyl)-7-octenoyl]-4-benzyl-1,3-oxazolidin-2-one (2.55 g, 7.70 mmol) in a 4:1 mixture of THF and H_2O was treated with 30% H_2O_2 (4.0 mL, 30.82 mmol), followed by LiOH (0.70 g, 15.41 mmol) at 0 °C. The resulting mixture was stirred and allowed to warm to room temperature overnight. THF was then removed under vacuum. The residue was washed with dichloromethane (50 mL x 2) to remove (S)-4-benzyl-oxazolidin-2-one. The desired product was isolated by EtOAc extraction of the acidified (pH 1~2) aqueous phase. No further purification was required. Standing under high vacuum yielded the title compound. MH^+ 173.

15 Intermediate 4

(2R)-2-(Hydroxymethyl)-N-benzoy-7-octenamide.

To a mixture of (2R)-2-(hydroxymethyl)-7-octenoic acid (1.12 g, 6.51 mmol), O-benzyl hydroxylamine hydrochloride (1.04 g, 6.51 mmol) and 4-dimethylamino-pyridine (1.90 g, 15.62 mmol) in dichloromethane (30 mL) at 0 °C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.50 g, 7.81 mmol). After stirring at room temperature overnight, the reaction was then quenched with 1N aqueous HCl solution (25 mL) and extracted using dichloromethane (25 mL x 2). The organic extracts were washed with water, brine, and dried over MgSO_4 . Removal of the solvent under reduced pressure yielded the title compound. MH^+ 278.

25

Intermediate 5

(3R)-3-(5-hexen-1-yl)-N-benzoy-2-azetidinone.

To a mixture of (2R)-2-(hydroxymethyl)-N-benzoy-7-octenamide (1.51 g, 5.47 mmol) and triphenylphosphine (1.72 g, 6.56 mmol) in THF (50 mL) was added dropwise diisopropyl azodicarboxylate (1.3 mL, 6.56 mmol) at 0 °C. The reaction mixture was stirred and allowed to warm to room temperature overnight. The reaction was then quenched with water (50 mL).

30

The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, and dried over MgSO₄. After removing the solvent under vacuum, the residue was purified by flash column chromatography (hexane:EtOAc 6/1) to provide the title compound. MH+ 260.

5

Intermediate 6

(2R)-2-({N-Benzoxymethyl)-7-octenoic acid.

To a mixture of (3R)-3-(5-hexen-1-yl)-N-benzoxymethyl-azetidinone (0.39 g, 1.52 mmol) in a mixture of THF-H₂O-MeOH (15 mL, 3:1:1 v/v) was added lithium hydroxide monohydrate (1.64 g, 15.2 mmol). After stirring at room temperature overnight, water (15 mL) was added to the mixture. The solution was acidified to pH 4 with 3N aqueous HCl solution. It was extracted with EtOAc (30 mL x 2). The combined organic layers were dried over MgSO₄. Removal of the solvent under vacuum provided the title compound. MH+ 278.

15 Intermediate 7

(2R)-2-({N-formyl-N-benzoxymethyl)-7-octenoic acid.

To a cold solution of HCO₂H (3.2 mL) and dichloromethane (10 mL) at 0 °C was added acetic anhydride (1.2 mL, 12.9 mmol). The mixture was stirred for 1 hour at 0 °C. To the resulting mixture was added slowly a solution of (2R)-2-({N-benzoxymethyl)-7-octenoic acid (358 mg, 1.29 mmol) in dichloromethane (10 mL). The mixture was stirred at 0 °C for 3 hours. The volatiles were removed by evaporation under vacuum. Dichloromethane (20 mL) was added to it. It was washed with brine (20 mL x 2), and dried over MgSO₄. Filtration and evaporation under vacuum provided the title compound. MH+ 306.

25 Intermediate 8

4-(3-Buten-1-yl)-6-(dimethylamino)-2-hydrazino-1,3,5-triazine.

To a cyanuric chloride (1.07 g, 5.80 mmol) in anhydrous benzene (10.7 mL) was added at 0 °C dropwise a solution of 3-butenylmagnesium bromide (0.5M in THF, 12.8 mL, 6.38 mmol). The resulting mixture was stirred at 0 °C for 3 hrs. To the mixture were added 1,4-dioxane (10 mL), DIPEA (1.1 mL), followed by addition of dimethylamine (2.0M in MeOH, 3.2 mL, 6.38 mmol) at 0 °C. The mixture was stirred and allowed to warm up to room temperature over 2

30

hours. Finally to it was added hydrazine hydrate (7.0 mL) at room temperature. The mixture was stirred at room temperature overnight. Then the volatiles were evaporated in vacuo. The residue was purified by HPLC to provide the title compound as a white solid. MH+ 209.

5 Intermediate 9

N-[(2R)-2-({2-[4-(3-Buten-1-yl)-6-(dimethylamino)-1,3,5-triazin-2-yl]hydrazino}carbonyl)-7-octen-1-yl]-N-benzoxycarbonylformamide.

To a mixture of (2R)-2-({N-formyl-N-benzoxycarbonyl-amino}methyl)-7-octenoic acid (233 mg, 1.121 mmol), 4-(3-buten-1-yl)-6-(dimethylamino)-2-hydrazino-1,3,5-triazine (342 mg, 1.121 mmol),
 10 NMM (0.62 mL, 5.61 mmol) and HOAt (183 mg, 1.345 mmol) in DMF (11 mL) at room temperature was added 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (258 mg, 1.345 mmol). After stirring at room temperature overnight, the reaction mixture was then purified by HPLC to afford the title compound as a white solid. MH+ 496.

15 Intermediate 10

N-[[[(5R)-16-(Dimethylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),10,14,16-tetraen-5-yl]methyl]-N-benzoxycarbonylformamide.

To a solution of N-[(2R)-2-({2-[4-(3-buten-1-yl)-6-(dimethylamino)-1,3,5-triazin-2-yl]hydrazino}carbonyl)-7-octen-1-yl]-N-benzoxycarbonylformamide (280 mg,
 20 0.566 mmol) in dichloromethane (225 mL, 0.0025M) at room temperature was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (2nd generation Grubbs catalyst, 48 mg, 0.057 mmol). The reaction mixture was stirred and heated to reflux for 48 hours, the solvent was evaporated in vacuo, and the residue was then purified by HPLC to afford the title compound
 25 as a white solid. MH+ 468.

Intermediate 11

4-(3-Buten-1-yl)-6-chloro-2-(methylthio)pyrimidine.

To a mixture of 4,6-dichloro-2-(methylthio)pyrimidine (5.20 g, 26.66 mmol) and
 30 tris(acetylacetonate)iron (III) (0.47 g, 1.33 mmol) in THF (130 mL) and DMP (13 mL) at 0 °C was added slowly 3-butenylmagnesium bromide (0.5M in THF, 56 mL, 28.0 mmol). The

reaction mixture was stirred overnight. After the reaction was completed, THF was removed by evaporation in vacuo. The residue was dissolved in dichloromethane (100 mL), and washed with water (50 mL x 2), dried over MgSO₄, filtered and evaporated in vacuo to provide the title compound. MH+ 215.

5

Intermediate 12

4-[6-(3-Buten-1-yl)-2-(methylthio)-4-pyrimidinyl]morpholine.

To a solution of 4-(3-buten-1-yl)-6-chloro-2-(methylthio)-pyrimidine (26.66 mmol) and DIPEA (5.1 mL, 29.33 mmol) in 1,4-dioxane (100 mL) at room temperature was added morpholine (2.6 mL, 29.33 mmol). The reaction mixture was stirred and heated at 80 °C overnight. After the reaction was completed, the volatiles were removed by evaporation in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 8:1 to 4:1) to provide the title compound. MH+ 266.

15 Intermediate 13

4-(3-Buten-1-yl)-6-(4-morpholinyl)-2-hydrazinopyrimidine.

To a solution of 4-[6-(3-buten-1-yl)-2-(methylthio)-4-pyrimidinyl]-morpholine (0.73 g, 2.75 mmol) in dichloromethane (20 mL) at room temperature was added mCPBA (1.42 g, 8.26 mmol). The reaction mixture was stirred at room temperature for an hour. After the reaction was completed, the mixture was washed with saturated aqueous NaHCO₃ solution (20 mL x 2). The organic layer was dried over MgSO₄ and filtered, evaporated in vacuo. The resulting compound was dissolved in MeOH (20 mL), and treated with hydrazine hydrate (8 mL) at room temperature overnight. After evaporation in vacuo, the residue was purified by HPLC to provide the title compound as a yellow solid. MH+ 250.

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Intermediate 14

4-(3-Buten-1-yl)-6-(2-furanyl)-2-(methylthio)pyrimidine.

To a solution of 4-(3-buten-1-yl)-6-chloro-2-(methylthio)-pyrimidine (0.79 g, 3.69 mmol), 2-furanylboronic acid (0.45 g, 4.06 mmol), aq. Na₂CO₃ solution (2M, 4.1 mL) in dioxane (37 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (0.21 g, 0.185 mmol). The reaction mixture in sealed tube was stirred and refluxed at 110 °C for 18 hours.

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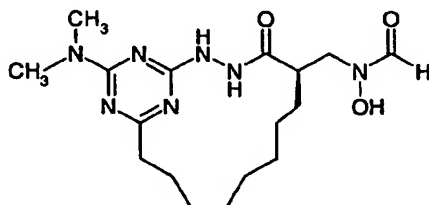
After the reaction was completed, the mixture was filtered through a pad of silica gel. The filtrate was evaporated in vacuo. The residue was dissolved in methylene chloride (30 mL). It was washed with water (30 mL x 2). The organic layer was dried over MgSO_4 and filtered, evaporated in vacuo. The residue was purified by column chromatography to provide the title compound. MH^+ 247.

Intermediate 15

6-Heptenoylhydrazine.

To a solution of 6-heptenoic acid (1.24 g, 9.68 mmol) in methylene chloride (40 mL) and MeOH (10 mL) was added slowly TMSCHN_2 (2M, 12.1 mL) at room temperature. The reaction mixture was stirred for additional 30 minutes. After the reaction was completed, the mixture was evaporated in vacuo. The residue was directly used for the next step without further purification. To the above residue in MeOH (20 mL) was added hydrazine monohydrate (5 mL) at room temperature. The reaction mixture was stirred at the same temperature overnight. The mixture was evaporated in vacuo. The residue was further dried by high vacuum overnight to provide the title compound. MH^+ 143.

Example 1



N-[[[(5R)-16-(Dimethylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide.

To a solution of N-[[[(5R)-16-(dimethylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),10,14,16-tetraen-5-yl)methyl]-N-benzyloxyformamide (75 mg) in MeOH (15 mL) was added 10% Pd/C (15 mg, 20% w/w). The reaction mixture was subjected to hydrogenation for 3 hours at room temperature. The reaction mixture was then filtered through a pad of Celite, and washed with MeOH (10 mL x 2). Removal of the solvent provided the title compound. MH^+ 380.

Example 2

N-([(5*R*)-16-(4-Morpholinyl)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide.

MH+ 422.

5

Example 3

N-([(5*R*)-16-(Cyclopropylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide.

MH+ 392.

10

Example 4

N-([(5*R*)-16-(4-Morpholinyl)-4-oxo-2,3,17,18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide.

MH+ 421.

15

Example 5

N-([(5*R*)-16-Methyl-4-oxo-2,3,17,18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl)methyl]-N-hydroxyformamide.

MH+ 350.

20

Example 6

N-([(5*R*)-4-Oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl]-N-hydroxyformamide.

MH+ 322.

25

Example 7

N-([(5*R*)-15-Methyl-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl]-N-hydroxyformamide.

MH+ 336.

30

Example 8

N-{[(5R)-15-(4-Morpholinyl)-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide.

5 MH+ 407.

Example 9

N-{[(5R)-15-(2-Furanyl)-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide.

10 MH+ 388.

Example 10

N-{[(5R)-15-(4-Morpholinyl)-4-oxo-2,3,14,16,17-pentaazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide.

15 MH+ 408.

Example 11

N-{[(5R)-15-(Dimethylamino)-4-oxo-2,3,14,16,17-pentaazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl}-N-hydroxyformamide.

20 MH+ 366.

Example 12

N-{[(5R)-4-Oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl}-N-hydroxyformamide.

25 MH+ 308.

Example 13

N-{[(5R)-14-Methyl-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl}-N-hydroxyformamide.

30 MH+ 322.

Example 14

N-[[*(5R)*-14-(Dimethylamino)-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl]methyl]-N-hydroxyformamide.

MH+ 351.

5

Example 15

N-[[*(5R)*-14-(4-Morpholinyl)-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl]methyl]-N-hydroxyformamide.

MH+ 393.

10

Example 16

N-[[*(4R)*-3,15-Dioxo-1,2-diazacyclopentadecan-4-yl]methyl]-N-hydroxyformamide.

MH+ 314.

15 COMPOSITIONS, ADMINISTRATION AND BIOLOGICAL ASSAYS

Compounds of Formula (1) and their pharmaceutically acceptable salts may be administered in a standard manner for antibiotics, for example orally, parenterally, sublingually, dermally, transdermally, rectally, via inhalation or via buccal administration.

20 Compositions of Formula (1) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules, creams and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers
25 include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example, using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example,
30 aqueous gums, celluloses, silicates or oils, and incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example, polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example, polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example, a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of Formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (1).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg of a compound of Formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg of a compound of Formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (1) are demonstrated by the following test:

Biological Assay.

5 S. aureus or E. coli PDF activity is measured at 25°C, using a continuous enzyme-linked assay developed by Lazennec & Meinnel ("Formate dehydrogenase-coupled spectrophotometric assay of peptide deformylase", Anal. Biochem. 1997, 244, pp.180-182), with minor modifications. The reaction mixture is contained in 50 uL with 50 mM potassium phosphate buffer (pH 7.6), 15 mM NAD, 0.25 U formate dehydrogenase. The substrate
10 peptide, f-Met-Ala-Ser, is included at the K_M concentration. The reaction is triggered with the addition of 10 nM Def1 enzyme, and absorbance is monitored for 20 min at 340 nm.

Antimicrobial Activity Assay.

Whole-cell antimicrobial activity was determined by broth microdilution using the
15 National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically" (incorporated by reference herein). The compound was tested in serial two-fold dilutions ranging from 0.06 to 64 mcg/ml. A panel of 12 strains were evaluated in the assay. This panel consisted of the following laboratory strains: Staphylococcus aureus Oxford,
20 Staphylococcus aureus WCUH29, Enterococcus faecalis I, Enterococcus faecalis 7, Haemophilus influenzae Q1, Haemophilus influenzae NEMC1, Moraxella catarrhalis 1502, Streptococcus pneumoniae 1629, Streptococcus pneumoniae N1387, Streptococcus pneumoniae N1387, E. coli 7623 (AcrABEFD+) and E. coli 120 (AcrAB-). The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that
25 inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

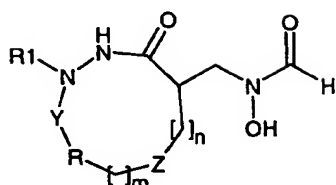
30 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are

within the scope of the following claims. Without further elaboration, it is believed that one skilled in the area can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the
5 invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to Formula (1):

5



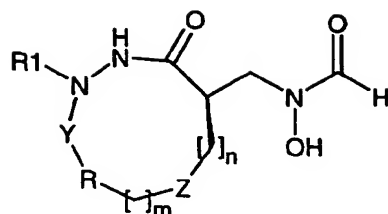
(1)

wherein:

- 10 Y represents $-\text{C}(\text{O})-$ or a covalent bond;
R represents a substituted arylene, a substituted heteroarylene or a covalent bond;
Z represents $-\text{CH}_2-$, $-\text{NR}_3-$, $-\text{O}-$, $-\text{C}(\text{O})\text{NR}_3-$, $-\text{NR}_3\text{C}(\text{O})-$ or $-\text{CH}=\text{CH}-$ when R is a substituted arylene or a substituted heteroarylene, and represents $-\text{CH}_2-$ or $-\text{CH}=\text{CH}-$ when R is a covalent bond; R₃ is hydrogen, C₁₋₃ substituted alkyl, and (CH₂)₀₋₂ C₃₋₆ substituted carbocycle;
- 15 R₁ is selected from the group consisting of:
hydrogen, C₁₋₃ substituted alkyl, C₂₋₃ substituted alkenyl, C₂₋₃ substituted alkynyl, and (CH₂)₀₋₂ C₃₋₆ substituted carbocycle;
- 20 m is equal to 0 when Z = $-\text{NR}_3-$ or $-\text{CH}_2-$; or m is equal to 0 or 1 when Z = $-\text{O}-$, $-\text{C}(\text{O})\text{NR}_3-$ or $-\text{NR}_3\text{C}(\text{O})-$; or m is an integer between 0 and 6 when Z = $-\text{CH}=\text{CH}-$;
- n is an integer equal to or greater than 2, appropriately chosen so that the number of atoms in the macrocyclic ring ranges from 13 to 16;
- or a salt, solvate, or physiologically functional derivative thereof.

25

2. A compound according to claim 1, wherein R₁ represents hydrogen;
3. A compound according to claim 2, with the following absolute configuration:



or a salt, solvate or physiologically functional derivative thereof.

5

4. A compound according to claim 3 selected from the group consisting of:

N-{[(5R)-16-(Dimethylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-16-(4-Morpholinyl)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-16-(Cyclopropylamino)-4-oxo-2,3,15,17,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-16-(4-Morpholinyl)-4-oxo-2,3,17,18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-16-Methyl-4-oxo-2,3,17,18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-4-Oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-15-Methyl-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-15-(4-Morpholinyl)-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-15-(2-Furanyl)-4-oxo-2,3,16,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl]methyl}-N-hydroxyformamide;

N-{[(5R)-15-(4-Morpholinyl)-4-oxo-2,3,14,16,17-pentaazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl]methyl}-N-hydroxyformamide;

N-([(5R)-15-(Dimethylamino)-4-oxo-2,3,14,16,17-pentaazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-yl)methyl]-N-hydroxyformamide;

N-([(5R)-4-Oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl]-N-hydroxyformamide;

5 N-([(5R)-14-Methyl-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl]-N-hydroxyformamide;

N-([(5R)-14-(Dimethylamino)-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl]-N-hydroxyformamide;

10 N-([(5R)-14-(4-Morpholinyl)-4-oxo-2,3,15,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-trien-5-yl)methyl]-N-hydroxyformamide; and

N-([(4R)-3,15-Dioxo-1,2-diazacyclopentadecan-4-yl)methyl]-N-hydroxyformamide.

5. A method of treating a bacterial infection by administering to a subject in need of treatment a compound according to claim 1.

15

ABSTRACT OF THE DISCLOSURE

Novel PDF inhibitors and novel methods for their use are provided.

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